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Relationship of Metabolic Syndrome With Incident Aortic Valve Calcium and Aortic Valve Calcium Progression

The Multi-Ethnic Study of Atherosclerosis (MESA)*

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OBJECTIVE—Metabolic syndrome (MetS) has been associated with increased prevalence of aortic valve calcium (AVC) and with increased progression of aortic stenosis. The purpose of this study was to determine whether MetS is associated with increased risks for the development of new ("incident") AVC or for progression of established AVC as assessed by CT.

RESEARCH DESIGN AND METHODS—The relationships of MetS or its components as well as of diabetes to risks for incident AVC or AVC progression were studied among participants with CT scans performed at baseline and at either year 2 or year 3 examinations in the Multi-Ethnic Study of Atherosclerosis (MESA).

RESULTS—Of 5,723 MESA participants meeting criteria for inclusion, 1,674 had MetS by Adult Treatment Panel III criteria, whereas 761 had diabetes. Among the 5,123 participants without baseline AVC, risks for incident AVC, adjusted for time between scans, age, sex, race/ethnicity, LDL cholesterol, lipid-lowering medications, and smoking, were increased significantly for MetS (odds ratio [OR] 1.67 [95% CI 1.21–2.31]) or diabetes (2.06 [1.39–3.06]). In addition, there was an increase in incident AVC risk with increasing number of MetS components. Similar results were found using the International Diabetes Federation MetS criteria. Among the 600 participants (10.5%) with baseline AVC, neither MetS nor diabetes was associated with AVC progression.

CONCLUSIONS—In the MESA cohort, MetS was associated with a significant increase in incident ("new") AVC, raising the possibility that MetS may be a potential therapeutic target to prevent AVC development. ***Diabetes*** **58:813–819, 2009**

Metabolic syndrome (MetS) is a collection of clinical and laboratory abnormalities comprised of central adiposity, hypertriglyceridemia, low HDL cholesterol, elevated blood pressure, and/or impaired fasting glucose (1,2). Overall MetS prevalence has been estimated at ~25% in Western populations (2,3) but is almost certainly increasing as a consequence of the worldwide epidemic of obesity (4,5). MetS is associated with both increased prevalence of coronary atherosclerosis (1,2,6,7) and increased risk for clinical cardiovascular events (8,9).

Cross-sectional U.S. data show that the prevalence of MetS increases with age (3), suggesting that MetS might contribute to risk for diseases with increased prevalence in the elderly. Examples of these diseases include both atherosclerosis (10) and calcific aortic valve disease (CAVD), which has a prevalence of 25% in those older than age 65 years (11). CAVD is comprised of aortic sclerosis, in which the valve is calcified and thickened but does not obstruct left ventricular outflow, and aortic stenosis, in which obstruction to left ventricular outflow is present (12,13). Aortic sclerosis is associated with an ~50% increase in cardiovascular events (14), and aortic stenosis is associated with a 5-year risk of 80% risk for valve replacement surgery or clinical cardiovascular events (15).

Previous studies have shown that the MetS and diabetes are associated with the presence of coronary artery calcium as assessed by cardiac CT (7). In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, in which the overall MetS prevalence by Adult Treatment Panel (ATP) III criteria is 21%, not only is MetS associated with increased prevalence of CT-detected aortic valve calcium (AVC), but also increased number of MetS features is associated with increased AVC prevalence (16). Metabolic syndrome also has been associated with increased progression of aortic stenosis (17) and accelerated degeneration of bioprosthetic aortic valves (18).

It is not known, however, whether abnormalities in glucose metabolism/insulin resistance, as typified by the clinical syndromes of MetS and diabetes, are associated with increased likelihood of incident ("new") AVC or AVC progression. We sought to evaluate potential associations of the MetS and diabetes both in the development of incident AVC as well as in the progression of established AVC using data from a multi-ethnic cohort of men and women, MESA.

RESEARCH DESIGN AND METHODS

Study population. The MESA cohort consists of 6,814 men and women, aged 45 to 84 years, recruited from six U.S. communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) and who were free of clinically evident cardiovascular disease at the time of enrollment (baseline). The main objective of MESA is to determine the characteristics of subclinical cardiovascular disease and its progression. Participants were excluded if they had a history of any of the following procedures: coronary bypass surgery, balloon angioplasty, heart valve replacement, pacemaker or defibrillator implantation, or history of any other cardiac surgery. The study was designed to include the following self-identified ethnic groups: whites, African Americans, Hispanics, and Chi-

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nese Americans. Sampling and recruitment procedures have been previously described in detail (19). Participants were enrolled between 1 August 2000, and 30 July 2002. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

Questionnaires were used to obtain information about socioeconomic status, medical history, medication, and tobacco use. Smoking was defined as current, former, or never. Waist circumference at the umbilicus was measured to the nearest 0.1 cm using a steel measuring tape (standard 4-ounce tension). Resting blood pressure was measured three times with participants in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). The average of the last two measurements was used in this analysis. Total and HDL cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-h fast. LDL cholesterol was calculated with the Friedewald equation (20).

Diabetes and metabolic syndrome. Participants were considered to have diabetes if they met the following criteria: self-reported history of adult onset of diabetes, fasting glucose 126 mg/dl or greater, or use of insulin or oral glucose-lowering medications.

Among those without diabetes, MetS was defined using ATP III (21)–modified criteria. These criteria require three or more of the following five criteria for MetS diagnosis: large waist circumference (women >88 and men >102 cm); elevated triglycerides (>150 mg/dl); low HDL cholesterol (men <40 and women <50 mg/dl); elevated blood pressure (>130/85 mmHg or self-reported use of medications for hypertension); and impaired fasting glucose (100–125 mg/dl) as defined in the updated American Heart Association/National Heart, Lung, and Blood Institute guidelines (1). Results also were analyzed using the International Diabetes Federation (IDF) definition of MetS.

Measurement of aortic valve calcium by CT. AVC was measured using either electron-beam tomography (three sites) or multidetector CT (three sites). A total calcium score was determined by summing individual lesion scores at each anatomic site. Any calcified focus seen extending to the aortic root was deemed AVC by methodology described previously (22–24). Calcification involving either the aortic or mitral annuli was not included. AVC score was assessed in every patient. The calcium score of each lesion was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield units within this area as described by Agatston (25). The absence of AVC was deemed a score of 0. Details of the scanning methodology used for AVC in the MESA study have been reported (23), and the median interscan variability for Agatston AVC scores within the MESA cohort is 6.4% (23). All studies were analyzed at the MESA CT reading center at Harbor-UCLA.

To define AVC progression, a second AVC measurement was performed on a random selection of half the cohort at exam 2 (September 2002 to January 2004) and on the other half of the cohort at exam 3 (March 2004 to July 2005). The mean time between scans was 2.4 (±0.9) years.

Data analyses. The study population for this analysis includes all MESA participants who had no missing data on any component of MetS with both baseline (exam 1) and follow-up (exam 2 or 3) CT scans. After applying these criteria, 5,723 individuals remained for analysis.

Participants were classified by the presence or absence of the MetS and diabetes, creating three groups (diabetes, MetS, and neither condition). Baseline demographics and laboratory measures were expressed with means and proportions and compared across groups using the χ^2 test and ANOVA. Because the exact date of development of incident AVC is not known, risk time was calculated as the elapsed time from the baseline to the second or third MESA examination. Unadjusted incident AVC rates were calculated as the number of events divided by person-years at risk, and incident AVC rates were examined according to the three groups of neither condition, MetS, or diabetes.

Two end points were created and modeled separately. The primary outcome of interest was incident progression of AVC defined as detectable AVC (AVC score >0) at follow-up (either exam 2 or 3) among those with no AVC (AVC = 0) at the baseline examination. This was treated as a dichotomous end point, and yearly incidence rates were calculated among the three groups. Logistic regression was used to evaluate the association between incident AVC and the MetS and diabetes groups. Unadjusted analyses were performed followed by multivariable modeling that included age, ethnicity, and time between scans. A second adjusted model added LDL cholesterol, lipid-lowering medication use, smoking status, and scanner type (to account for scanner changes that were made at some of the sites).

A secondary outcome looked at AVC progression defined as an absolute change in AVC score among those with detectable AVC at exam 1. The absolute change was calculated as the difference between AVC score at follow-up and baseline. This was treated as a continuous end point for which we found that ~62 participants (10.3%) had very large residuals and therefore used robust linear regression to downweight their influence (26,27). The same modeling strategy used for incident AVC, as described, was used for AVC progression with additional adjustment for baseline AVC score.

We also looked at the number of MetS risk factors while treating diabetes as a separate category in order to explore relative associations of individual MetS components and of the number of components with incidence and progression of AVC using those with 0 MetS risk factors as the reference group. Because the numbers of participants who had four or five risk factors were relatively small, they were grouped together.

Interactions were evaluated between the three groups and each sex as well as between the three groups and each race. A P value ≤0.05 was considered statistically significant. Statistical analyses were performed with S-Plus (release 6.1; Insightful, Seattle, WA) and SPSS 15.0.1 software for Windows (SPSS, Chicago, IL).

RESULTS

Participant characteristics. The study population for these analyses included 5,723 MESA subjects with a mean age of 62 years (SD = 10); 52% were female, 27% were African American, 12% were Chinese, and 22% were Hispanic. Of these, 1,674 (29%) met the ATP III definition for MetS and an additional 761 (13%) met the definition for diabetes. Table 1 shows the distribution of demographics and components of the MetS by MetS and diabetes groups. Participants with neither MetS nor diabetes were more likely to be younger; have lower values for BMI, triglycerides, and systolic blood pressure; and higher values for HDL. Large waist circumference was the most common component for the MetS (83%), whereas high blood pressure was the most common component for diabetes (77%).

Of the 5,123 participants with an AVC of 0 at baseline, 211 (4%) developed an AVC greater than 0 over follow-up (new "incident" AVC). The breakdown by condition is 88 (3%) for neither MetS nor diabetes, 79 (5%) for MetS, and 44 (7%) for diabetes ($P < 0.0001$). At baseline, there were 600 (11%) participants with AVC greater than 0 who were, therefore, classified as at risk for AVC progression. Of these, 266 (8%) had neither MetS nor diabetes, 204 (12%) had MetS only, and 130 (17%) had diabetes ($P < 0.001$). The median baseline AVC score for these 600 participants was 68 Agatston units (interquartile range [IQR] 25–152). The median (IQR) baseline AVC scores were, by condition, 54 (22–144) for neither MetS nor diabetes, 80 (25–178) for MetS, and 63 (27–113) for diabetes ($P = 0.335$).

Incident AVC

Rates for incident AVC by metabolic syndrome, diabetes, or neither condition. Incident ("new") AVC was higher among those with either MetS or diabetes as compared with those with neither condition. The yearly rate of incident AVC per 100 person-years (among participants without AVC at baseline) in subjects with the MetS was lower than in those with diabetes (Fig. 1, *left*). Rates of incident AVC were 2.2% per year in those with ATP III–defined MetS and 3.0% per year in those with diabetes as compared with 1.2% per year in those with neither ($P = 0.0001$ for ATP III MetS versus neither condition and $P < 0.0001$ for diabetes versus neither condition). Similar results were obtained using the IDF criteria for MetS (Fig. 1, *right*). There was no sex or race interaction for the relationship of either MetS or diabetes with incident AVC (P for interaction = 0.633 and 0.581, respectively).

Rates of incident AVC by number of MetS components. There was a graded, linear association between the rate of incident AVC and the number of MetS components. Those with diabetes had the highest rates of incident AVC (Fig. 2).

TABLE 1
Characteristics of participants with diabetes, ATP III–defined MetS, or neither condition

	Neither condition	MetS	Diabetes	*P*
n	3,288	1,674	761	
Age (years)	61 ± 10	63 ± 10	65 ± 9	<0.001
Men	1,601 (49)	716 (43)	406 (53)	<0.001
Race/ethnicity				<0.001
Caucasian	1,440 (44)	677 (40)	151 (20)	
Chinese American	428 (13)	151 (9)	95 (13)	
African American	823 (25)	435 (26)	285 (38)	
Hispanic	597 (18)	411 (25)	230 (30)	
Glucose (mg/dl)	93 ± 9	101 ± 10	155 ± 53	<0.001
BMI (kg/m^2)	26.5 ± 4.7	30.9 ± 5.2	30.6 ± 5.7	<0.001
Total cholesterol (mg/dl)	194 ± 33	196 ± 36	189 ± 39	<0.001
HDL cholesterol (mg/dl)	56 ± 15	44 ± 11	46 ± 12	<0.001
LDL cholesterol (mg/dl)	118 ± 30	117 ± 31	112 ± 33	0.111
Triglycerides (mg/dl)	93 (68–124)	162 (112–210)	134 (87–199)	<0.001
Lipid-lowering medications	393 (12)	326 (20)	206 (27)	<0.001
Diastolic blood pressure (mmHg)	71 ± 10	74 ± 10	72 ± 10	<0.001
Systolic blood pressure (mmHg)	121 ± 20	133 ± 21	132 ± 21	<0.001
Antihypertensive medications	714 (22)	821 (49)	465 (61)	<0.001
Current smoker	405 (12)	229 (14)	91 (12)	0.556
Metabolic syndrome components*				
Abdominal obesity (large waist)	1,140 (35)	1,393 (83)	518 (68)	<0.001
High blood pressure	1,263 (38)	1,301 (78)	584 (77)	<0.001
LDL cholesterol	547 (17)	1,119 (67)	385 (51)	<0.001
High triglycerides	359 (11)	994 (59)	334 (44)	<0.001
Impaired fasting glucose (100–125 mg/dl)†	568 (17)	1,013 (61)	0 (0)	<0.001

Data are *n* (%), means ± SD, or means (interquartile range). *At least three of the five following conditions define presence of MetS: high blood pressure, low HDL cholesterol, high triglycerides, impaired fasting glucose, or large waist. †American Diabetes Association definition of impaired fasting glucose.

Multivariable analyses: odds ratios for incident AVC. In logistic regression analyses adjusted for age, sex, ethnicity, and time between scans, the odds ratios (ORs) for incident AVC were significantly higher in participants with either the MetS (1.73 [95% CI 1.25–2.38]) or diabetes (2.16 [1.46–3.19]) as compared with those with neither condition. These associations persisted after additional adjustment for LDL cholesterol, lipid-lowering medication use, and smoking (MetS, OR 1.67 [1.21–2.31], and diabetes, 2.06 [1.39–3.06]) (Table 2).

Risks for incident AVC by number of MetS components. When examining the ORs for incident AVC by number of MetS components (Fig. 3), a similar pattern emerged. As compared with those with no MetS components, participants with three MetS risk factors, four to five MetS risk factors, and diabetes had a significantly increased risk of incident AVC in a model adjusted for age, sex, ethnicity, time between scans, LDL cholesterol, use of lipid-lowering medication, and smoking (OR, 1.88 [95% CI 1.01–3.51], 2.24 [1.16–4.30], and 2.50 [1.32–4.73], respectively).

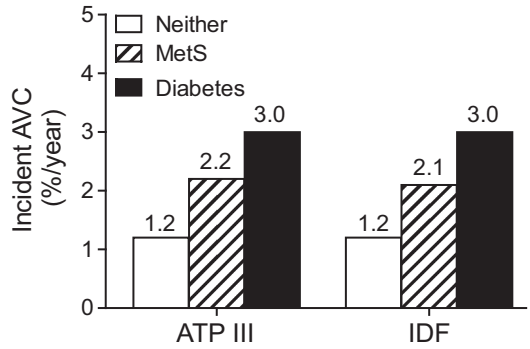

FIG. 1. Rates of incident AVC for diabetes (■), MetS (▨), or neither condition (□) using MetS criteria as defined by ATP III (*left*) or IDF (*right*).

Incident AVC and individual MetS components. We evaluated the association of individual components of the MetS with incident AVC (Table 3) in those participants without diabetes. Each of the five MetS components was added in the model simultaneously, and the model was then further adjusted for age, sex, ethnicity, time between scans, LDL cholesterol, lipid-lowering medication, and smoking. Incident AVC was only related to low HDL (adjusted OR 1.54 [95% CI 1.08–2.19]). In both unadjusted and demographic-adjusted analyses, there were associations between impaired fasting glucose and incident AVC, but these associations were attenuated and of marginal statistical significance after multivariable adjustment (1.36 [0.97–1.90]).

Given the strong relationship of AVC among those with diabetes, we also looked at the association of continuous glucose (per 10 mg/dl). For participants without diabetes, the unadjusted model showed a strong increased risk between glucose and incident AVC (OR 1.33 [95% CI 1.14–1.55]). Although this risk was attenuated after full adjustment, it remained significantly elevated (1.18 [1.01–1.40]).

AVC progression. Among those with AVC at baseline (n = 600), the median (IQR) annualized rate of AVC score change was 5.4 (−2.0 to 23.0) Agatston units per year. The rate of AVC score change did not vary significantly by MetS or diabetes status (P = 0.341 by Kruskal-Wallis) (Fig. 4). When examining the median AVC change by number of

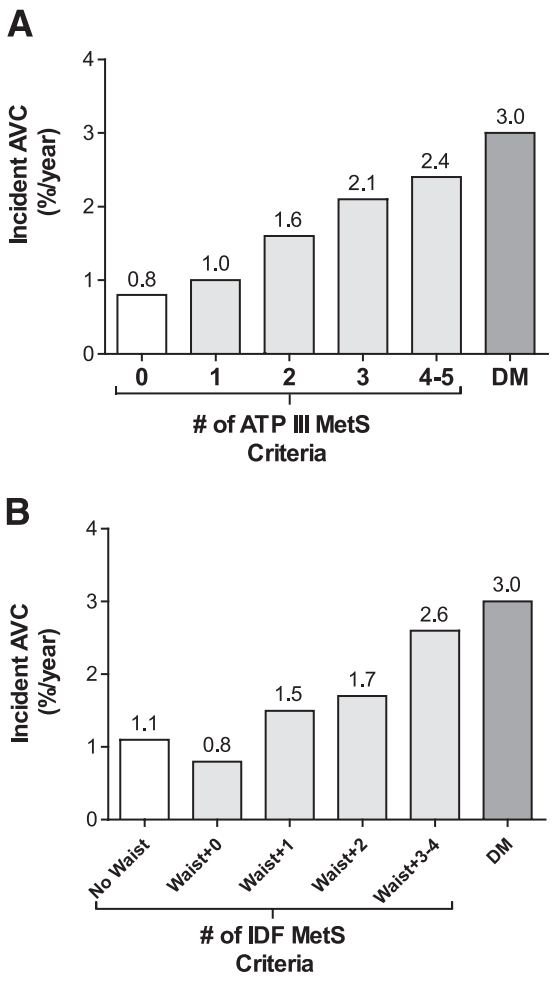

FIG. 2. Rates of incident AVC by number of MetS components as defined by ATP III criteria (*A*) or IDF criteria (*B*). DM, diabetes.

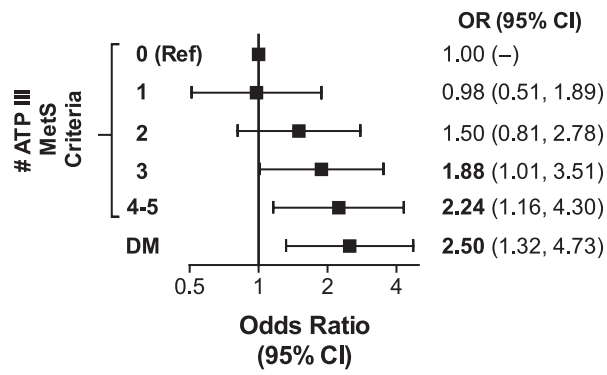

FIG. 3. Adjusted ORs (*boxes*) and corresponding 95% CIs (*bars*) for incident AVC by number of ATP III MetS criteria or diabetes (DM).

MetS components, no pattern emerged ($P = 0.634$ by Kruskal-Wallis, results not shown). Adjusted robust regression also showed that there was no significant AVC progression in Agatston units per year for either the MetS or diabetes compared with neither condition (results not shown).

DISCUSSION

Only one prospective study has demonstrated an association of MetS with increased risk for prevalent AVC (16), whereas retrospective studies have demonstrated that MetS is associated with increased rates of aortic stenosis progression (17) and bioprosthetic valve deterioration (18). AVC incidence is more important than prevalent AVC because it provides stronger evidence in establishing causality. By separating predictor and outcome variable over time, the longitudinal analysis reduces systematic bias and enhances causal inference. The present study is the first to prospectively examine the relationship of MetS to risks for incident ("new") AVC and AVC progression. In fully adjusted analyses, both MetS and the number of MetS components were associated strongly with increased risk for incident AVC. We did not, however, identify an association of either MetS or diabetes with the rate of AVC progression.

The relationship of advanced dysglycemia, that is, clinical diabetes, to aortic valve disease pathology has been demonstrated in previous small, retrospective studies reporting associations of diabetes with increased prevalence of AVC (28) as well as with increased prevalence (29) and progression (30) of aortic stenosis. We and others have extended the relationship of less severe dysglycemia, that is, MetS, to aortic valve disease pathology by demonstrating that MetS is associated not only with increased prevalence of AVC (16), but also with faster aortic stenosis progression (17) and more rapid deterioration of bioprosthetic aortic valves (18). The results of the present study further extend the relationship of MetS to early-stage aortic valve disease pathology by demonstrating that MetS and MetS components are associated with an increased rate of new ("incident") AVC. In our study, participants with diabetes and the MetS had the highest prevalence of new ("incident") AVC.

The association of the dysglycemias, including diabetes and MetS, with increased risks for prevalent vascular (6,7) and valvular (16) calcification has been established, and interesting studies have begun to elucidate potential mechanisms that may underlie these associations. The key osteogenic regulatory factor, bone morphogenic protein (BMP)2, is upregulated by hyperglycemia in vitro. (31,32) BMP2 has been demonstrated to play a role in vascular calcification (33,34) and has been detected in areas of valvular calcification (35). BMP2 upregulates both "osteogenic" differentiation regulated by the transcription factor Msx2 and "chondro-ostegenic" differentiation regulated by the transcription factor Runx2/Cbfa1 (36).

Diabetes is characterized by a pro-oxidant state (37,38). Not only are oxidized lipoproteins present in human aortic valve lesions (39), but oxidized lipids also have been shown to upregulate the rate of calcium nodule formation in valvular cells in vitro (40). Several potential mecha-

TABLE 2
Logistic regression models for the risk of incident AVC (among those free of AVC at baseline) and diabetes, MetS (by ATP III criteria), or neither condition

	Neither condition	MetS	Diabetes
n	3,022	1,470	631
Unadjusted	1.0 (ref.)	1.84 (1.35–2.53)	2.54 (1.75–2.53)
Adjusted*	1.0 (ref.)	1.73 (1.25–2.38)	2.16 (1.46–3.19)
Adjusted†	1.0 (ref.)	1.67 (1.21–2.31)	2.06 (1.39–3.06)

Data are OR (95% CI). *Adjusted for time between scans, age, sex, and race/ethnicity. †Adjusted for time between scans, age, sex, race/ethnicity, scanner type, LDL cholesterol, lipid-lowering medications, and smoking.

TABLE 3
Logistic regression models for the risk of incident AVC (among those free of AVC at baseline) for each component of the MetS in participants free of diabetes

	OR (95% CI)		
	Adjusted*	Adjusted†	Adjusted‡
Elevated blood pressure	1.37 (0.96–1.95)	1.34 (0.94–1.91)	1.25 (0.87–1.79)
LDL cholesterol	1.64 (1.18–2.28)	1.63 (1.17–2.27)	1.54 (1.08–2.19)
High triglycerides	1.25 (0.87–1.80)	1.22 (0.85–1.76)	0.96 (0.65–1.42)
Impaired fasting glucose (≥100 mg/dl)	1.53 (1.10–2.12)	1.49 (1.07–2.07)	1.36 (0.97–1.90)
Abdominal obesity	1.41 (1.00–1.99)	1.39 (0.98–1.96)	1.20 (0.83–1.72)

*Adjusted for time between scans, age, sex, and race/ethnicity. †Adjusted for time between scans, age, sex, race/ethnicity, scanner type, LDL cholesterol, lipid-lowering medications, and smoking. ‡Adjusted further for components of the MetS.

nisms may contribute to the increased risk of incident AVC seen with metabolic syndrome and diabetes.

These observational findings also are interesting in light of the recent demonstration that an elevated total-to-HDL cholesterol ratio is associated with a consistent increase in relative risk for AVC across all ages in the MESA cohort (41). Clinical abnormalities of glucose metabolism (which include impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes) are associated with both a progressive increase triglyceride-rich VLDL cholesterol and a progressive decrease in HDL cholesterol (8). Together, these changes increase the total-to-HDL cholesterol ratio (42). Retrospective studies had suggested a potential benefit of statin therapy (which primarily lowers LDL levels) in aortic valve disease (43–46). The results of subsequent, properly controlled clinical trials of atorvastatin (47) or of simvastatin plus ezetimibe (48) have been convincingly negative despite average therapy-related LDL reductions of over 50% in both trials. Because the characteristic MetS lipid abnormalities of high triglycerides and low HDL result in an increase in the total-to-HDL cholesterol ratio, it is not known whether more specifically targeting this MetS-associated dyslipidemia might represent an effective strategy for decreasing the MetS-associated risks for incident AVC.

Recent studies have implicated the renin-angiotensin system, which is upregulated in MetS (2) in aortic valve disease pathogenesis (49–52). Retrospective studies of ACE inhibitor therapy have been mixed in the general population of individuals with aortic sclerosis (50) or aortic stenosis (46). The results of the present study, however, raise the possibility that renin-angiotensin system inhibitor therapy targeted to those with MetS might prove effective at slowing the rate of development of CAVD.

The association of progressive increase in plasma glucose with progressive increase in risk for incident AVC risk raises the possibility that dysglycemia may represent an additional therapeutic target in this disease, as has been demonstrated for atherosclerosis (53).

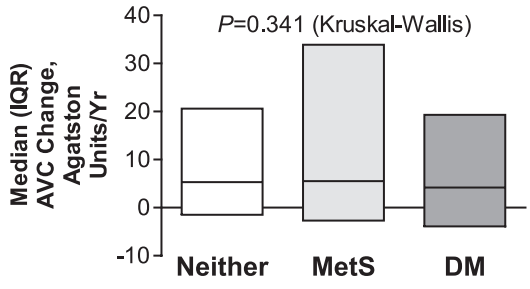

FIG. 4. Median AVC change by diabetes, MetS, or neither condition. "Box" plots the median AVC progression score (*middle horizontal lines*) in Agatston units/year and corresponding 25th (*lower bound of box*) and 75th (*upper bound of box*) percentile ranges.

This study has limitations, which include the possibility of survival bias, because those with clinical cardiovascular disease were excluded from MESA; limited statistical power, because the exclusion of those with known cardiovascular disease from MESA may have also resulted in the exclusion of individuals with MetS (1,2) and AVC (16), thereby limiting our power to show a relationship between MetS and AVC progression; dichotomization of continuous measures such as MetS components, which may decrease available information and result in misclassification of exposure; and survival bias attributed to participants who did not attend the follow-up examinations; and given the relatively short follow-up time, it is possible that AVC may not have developed between visits or AVC may not have been captured by CT scans. Nonetheless, MetS is defined using cut points in clinical practice. It is reassuring that similar results were found using both ATP III and IDF MetS criteria. Strengths of this study include use of a large, well-characterized, population-based cohort and of a highly reproducible technique for quantifying AVC.

This study formally tests the hypothesis that MetS is associated with increased risk for the development of AVC. These findings further underscore the clinical importance of identifying MetS in populations without clinical cardiovascular disease and, further, raise the possibility of screening for the presence of aortic valve disease in those with MetS. These findings suggest that future studies targeting the MetS-associated "atherogenic dyslipidemia" of high triglycerides and low HDL cholesterol as well as renin-angiotensin system components and/or insulin resistance may identify useful strategies to decrease the development of aortic valve disease.

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